

### **Remarks**

After entry of the amendments herein, claims 1, 3-5, 7, 10, 14-16 are pending. Claims 2, 6, 8, 9, 12 and 13 have been canceled herein. Claims 1, 3, 4, and 14 have been amended and claim 16 is newly added. Support for these amendments may be found at least at in the original claims.

### ***Rejections Under Section 112, Second Paragraph***

Claims 1-10 and 12-15 were rejected under § 112, second paragraph as indefinite for various reasons. First, the claims were rejected for the use of improper Markush language. Applicants have amended the claims and therefore request that the rejection be withdrawn.

Second, the claims were rejected as indefinite for the use of the terms "a nitrogen protecting group" and "an oxygen protecting group". The examiner indicated that it was unclear from what the compounds needed protection. Applicants have amended claim 1 to delete the terms and request that the rejection be withdrawn with respect to claim 1 and its dependent claims.

Applicants have added a new claim (claim 16) directed to protected forms of the compound of claim 1. Applicants respectfully submit that claim 16 is not indefinite as the terms are defined in the specification at page 5, line 25 to page 6, line 26. According to the MPEP,

[t]he essential inquiry pertaining to [the definiteness] requirement is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of:

- (A) The content of the particular application disclosure;
- (B) The teachings of the prior art; and
- (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

(MPEP 2173.02). One of ordinary skill in the art would understand what was meant by the terms "nitrogen protecting group" and "oxygen protecting group" particularly when viewed in light of the specification which clearly defines the terms. Applicants respectfully request that the rejection be withdrawn as the terms meet the requirements of § 112, second paragraph.

Third, claim 8 was rejected as indefinite because it omitted essential steps. Without acquiescing to the propriety of the rejection, Applicants have canceled claim 8 herein and therefore request that the rejection be withdrawn.

Fourth, claim 12 was rejected as indefinite because the scope of the claim was not ascertainable. Without acquiescing to the propriety of the rejection, Applicants have canceled claim 12 herein and therefore request that the rejection be withdrawn.

***Rejections Under Section 112, First Paragraph***

Claims 1-10 and 12-15 stand rejected under § 112, first paragraph as not enabling for solvates of the compound of Formula I. The examiner asserts that applicants have not shown how one skilled in the art can arrive at a given solvate. In addition, the examiner asserts that arriving at a given solvate is not routine experimentation because it is unpredictable and one cannot make any solvate of a given compound. For the reasons stated below, Applicants respectfully disagree with this conclusion and instead assert that the claims in their current form are fully enabled commensurate with their scope.

The test for enablement is whether the disclosure, when filed, contained sufficient information to enable one of ordinary skill in the art to make and use the claimed invention without undue experimentation. MPEP 2164.01.

The Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'." *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Nevertheless, not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See, e.g., *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

MPEP 2164.08 (emphasis added).

"In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure)." MPEP 2164.04. "[I]t is incumbent upon the Patent Office, whenever a rejection [for lack of enablement] is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971).

In this case, the examiner has not met the initial burden of establishing a reasonable basis for doubting the enablement of the claimed invention. The examiner has not provided any evidence that one of ordinary skill in the art would not be able to form the claimed solvates without undue experimentation. The mere failure to include working examples that describe formation of solvates of the claimed compound does not, as the examiner purports, mean that these forms of the compound do not exist.

In general, the disclosure of the novel compound of the claimed invention is more than sufficient to enable those having ordinary skill in the art to make and use the compound as well as any solvates thereof. Applicants respectfully submit that one of ordinary skill in the art would be capable of making a solvate of the claimed compound without undue experimentation, especially given the level of ordinary skill in the art. Thus, it is applicants' position that the scope of enablement provided in the specification bears a more than "reasonable correlation" to the scope of claims 1-10 and 12-15.

Moreover, contrary to the examiner's position, the specification specifically teaches solvates of the claimed compound where the solvent adds across the imine bond of the pyrrolobenzodiazepine moiety. If the solvent is water or an alcohol, these solvates can be called the carbinolamine and carbinolamine ether forms of the pyrrolobenzodiazepine. (Specification at page 28, line 30 to page 29, line 10). Moreover, one of ordinary skill in the art would have known that any nucleophilic solvent, such as thiols and amines, is capable of forming such a solvate. (Specification at page 29, lines 11-14).

Thus, applicants respectfully submit that the claims are fully enabled by the specification and request that the rejection be withdrawn.

Claim 13 is also rejected as not enabled because the examiner asserts that the specification does not provide enablement for treatment of a proliferative disease generally. Without acquiescing to the propriety of the rejection, Applicants have canceled claim 13 herein and therefore request that the rejection be withdrawn.

***Objection Under 37 CFR 1.75***

The examiner indicated that claim would be objected to as a substantial duplicate of claim 1 if claim 1 was found to be allowable. Applicants have canceled claim 9 herein.

### **Section 103 Rejections**

Claims 1, 6-10 and 12-15 were rejected under § 103(a) as being unpatentable over Thurston et al. (WO 93/18045). Thurston et al. are cited as teaching a genus of pyrrolobenzodiazepines that embraces the claimed compounds. The Office Action admits that the claims are directed to specific species and a narrower genus than Thurston et al. disclose.

The present application is drawn to a specific compound within the genus of Thurston et al. The compounds of Examples 4 and 6 of Thurston et al. are the most similar to the claimed compound. The compound of Example 4 differs from the claimed compound in that it does not have any substitution on the C-ring. The compound of Example 6 differs from the claimed compound in that it has a three-carbon chain linking the PBD-oxy moieties. The compound of Example 4 has an IC<sub>50</sub> of about 0.5 micromolar in K562 cells and the compound of Example 6 has an IC<sub>50</sub> of about 0.01 micromolar. (Thurston et al. at page 40).

Applicants respectfully submit that the Office Action has not set forth a *prima facie* case of obviousness. Post-KSR, the Federal Circuit stated that: "in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound." *Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007). The Examiner has not provided any rationale why one of ordinary skill in the art would have modified the compounds of Thurston et al. to arrive at the claimed invention. The Examiner is impermissibly using hindsight and the Applicant's disclosure to piece together an obviousness rejection. The MPEP states that a statement by the Examiner that modifications of the prior art to meet the claimed invention would have been "well within the ordinary skill of the art at the time the claimed invention was made" because the references relied upon teach that all aspects of the claimed invention were known is not sufficient to establish a *prima facie* case of obviousness without some objective reason to modify the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). As pointed out by the Supreme Court recently, "[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR*, 550 U.S. at \_\_\_, 82 USPQ2d at 1396 quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). Thus, it is not sufficient to state that the motivation arises from the assumption that compounds of similar structures will have similar properties. *Takeda*, 492 F.3d 1350. The

Examiner has not provided any rationale beyond a conclusory statement for modifying the compounds of Thurston et al.

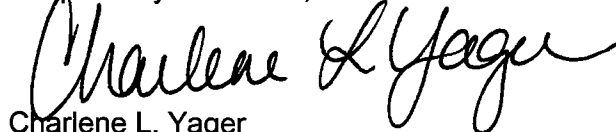
Moreover, it is unpredictable and unobvious whether or not such changes in a pyrrolobenzodiazepine would affect the ability of the compound to bind to DNA. The chance of chemical and structural differences causing decreased or eliminated ability to bind to DNA relative to those compounds disclosed by Thurston et al. is just as great as the chances of them causing enhanced or equal ability to bind to DNA. The claimed compound has an  $IC_{50}$  value of about 0.05 nanomolar. (Specification at page 41). Thus, the claimed compound is significantly better than the compounds of Thurston et al. This is not a predictable result and there would not have been a reasonable expectation of success.

The Applicants respectfully submit that the examiner has not established either a motivation to modify the compounds of Thurston et al. to arrive at the claimed compound or a reasonable expectation of success that the claimed compound would have the same function as the compounds of Thurston et al. Thus, Applicants respectfully request withdrawal of the rejection over Thurston et al.

### **Conclusion**

Applicants respectfully submit that the claims are in condition for allowance. Should the examiner feel that any issues remain or wish to discuss anything further, the examiner is invited to contact the undersigned at the number below. No fee is believed due in connection with the above response. Should any fee, in fact, be due, please charge Deposit Account No. 50-0842.

Respectfully submitted,



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